Doppler Indexes of Left Ventricular Systolic and Diastolic Flow and Central Pulse Pressure in Relation to Renal Resistive Index

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BACKGROUND
The cardio-renal interaction occurs via hemodynamic and humoral factors. Noninvasive assessment of renal hemodynamics is currently possible by assessment of renal resistive index (RRI) derived from intrarenal Doppler arterial waveforms as ((peak systolic velocity − end-diastolic velocity)/peak systolic velocity). Limited information is available regarding the relationship between RRI and cardiac hemodynamics. We investigated these associations in randomly recruited subjects from a general population.

METHODS
In 171 participants (48.5% women; mean age, 52.2 years), using pulsed wave Doppler, we measured RRI (mean, 0.60) and left ventricular outflow tract (LVOT) and transmitral (E and A) blood flow peak velocities and its velocity time integrals (VTI). Using carotid applanation tonometry, we measured central pulse pressure and arterial stiffness indexes such as augmentation pressure and carotid–femoral pulse wave velocity.

RESULTS
In stepwise regression analysis, RRI independently and significantly increased with female sex, age, body weight, brachial pulse pressure, and use of β-blockers, whereas it decreased with body height and mean arterial pressure. In multivariable-adjusted models with central pulse pressure and arterial stiffness indexes as the explanatory variables, we observed a significant and positive correlation of RRI only with central pulse pressure ($P < 0.0001$). Among the Doppler indexes of left ventricular blood flow, RRI was significantly and positively associated with LVOT and E peak velocities ($P \leq 0.012$) and VTIs ($P \leq 0.010$).

CONCLUSIONS
We demonstrated that in unselected subjects RRI was significantly associated with central pulse pressure and left ventricular systolic and diastolic Doppler blood flow indexes. Our findings imply that in addition to the anthropometric characteristics, cardiac hemodynamic factors influence the intrarenal arterial Doppler waveform patterns.

Keywords: artery stiffness; blood pressure; Doppler cardiac flow; hypertension; population; pulse pressure; renal resistive index.

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Cardiovascular system and kidney function are tightly linked. This cardio-renal interaction occurs primarily via hemodynamic factors but also via endogenous humoral factors that are associated with acute or chronic damage of the kidney and/or heart. Furthermore, cardiovascular and renal diseases share the same risk factors, including hypertension, glucose intolerance, obesity, etc.[1,2]

Noninvasive assessment of renal hemodynamics is currently possible by analyzing the intrarenal arterial waveforms as measured by Doppler ultrasound. The renal resistive index (RRI), derived from the Doppler pulsatile flow-velocity waveform as ((peak systolic velocity − end-diastolic velocity)/peak systolic velocity), is the most described measure in renal Doppler ultrasonography.[3] Over the last years, RRI has been intensively studied to gain diagnostic and prognostic insights into a variety of renal clinical conditions such as assessment of renal allograft rejection,[4,5] detection and management of renal artery stenosis in hypertensive patients,[6,7] evaluation of progression in chronic kidney disease,[8] and prediction of renal and composite adverse outcomes in critically ill patients.[9,10]

Although RRI was initially considered to reflect only intrarenal vascular pathological processes, this index is a product of a complex interaction of vascular wall properties and systemic hemodynamic factors, yet most of these factors are insufficiently understood.[3] Recently, a large community-based study reported anthropometric and hemodynamic determinants of RRI such as age, body mass index, and systolic and diastolic blood pressure (BP).[11] Moreover, in hypertensive patients, increased RRI was independently associated with target organ damage, such as left ventricular (LV) hypertrophy and carotid intima–media thickness.[12–14]

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To our knowledge, no community-based study explored the relationship of RRI with cardiac hemodynamics. The objectives of the present research were, therefore, to describe in a randomly recruited population sample the determinants of RRI and to investigate the relation of RRI with echocadiographic indexes of left ventricular systolic and diastolic function, central hemodynamics, and arterial characteristics.

METHODS

Study participants

This study is nested in the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO), a large family-based population resource on the genetic epidemiology of cardiovascular phenotypes, for which recruitment started in 1985 and continued through 2010. The selection criteria and study design are detailed in the online Data Supplement Methods section. The Ethics Committee of the University of Leuven approved the study and participants provided informed consent.

The FLEMENGHO study is an on-going longitudinal population study and, therefore, the participants were repeatedly visited at home and examined at a local examination center. From October 2012 until June 2013, a scheduled follow-up examination included also renal Doppler ultrasound. From 247 invited participants for this examination, we obtained informed written consent from 181 subjects (response rate 73.3%). Because Doppler renal waveform was of insufficient quality to assess RRI, we discarded 7 subjects from the analysis. Furthermore, 1 participant with atrial fibrillation, 1 renal donor, and 1 person with 2-sided polycystosis were excluded. Thus, the number of participants statistically analyzed totaled 171. In 4 participants, Doppler measurements have been done on 1 kidney because of presence of significant renal pathology at the other kidney including kidney stones, renal cysts, hydronephrosis, and polycystosis.

Renal Doppler ultrasound

The participants refrained from smoking, heavy exercise, and drinking alcohol or caffeine-containing beverages for at least 3 hours before ultrasound examination. The BP was the average of 2 readings, obtained with a validated OMRON 705IT device (Omron Corp., Tokyo, Japan) at the end of the ultrasound examination.

Renal gray scale and color Doppler ultrasounds were performed by 1 experienced observer (T.K.), using a Vivid E9 ultrasound scanner (GE Vingmed, Horten, Norway) interfaced with a 1.5- to 4.5-MHz convex transducer according to a standardized procedure.[11,15] Renal imaging was performed with participants in the supine position or, in case of insufficient image quality, in the left or right decubitus position. Intrarenal blood flow of at least 3 segmental/interlobal arteries (superior, middle, and inferior) in each kidney was recorded using Doppler ultrasonography. All recordings included at least 5 cardiac cycles and were digitally stored for off-line analysis.

Two observers independently post-processed renal images of each participant using the EchoPAC software version 112. The RRIs were computed using at least 3 segmental/interlobal arterial waveforms in each kidney as ((peak systolic velocity − end-diastolic velocity)/peak systolic velocity). The average value of the 2 observers' measurements was used for statistical analysis.

To determine interobserver variability, RRIs were measured in duplicates by 2 observers in 20 subjects. The interobserver variability was estimated using the Bland and Altman's approach.[16] The absolute and relative differences between 2 observers for RRI were 0.001 ± 0.038 and $-0.01 \pm 6.46\%$, respectively (Supplementary Figure S1, panels A and B). Interobserver correlation coefficient for RRI was 0.93 for both kidneys (Supplementary Figure S1, panel C).

Echocardiography

The complete echocardiographic protocol and reproducibility study are provided in the Data Supplement. Briefly, the same experienced physician (T.K.) did the ultrasound examination, using a Vivid E9 (GE Vingmed) interfaced with a 2.5- to 3.5-MHz phased-array probe.[17] All digitally stored images were analyzed, averaging 3 heart cycles for statistical analysis, using a workstation running the EchoPAC, version 112 software package (GE Vingmed). LV mass index (LVMI) was LV mass divided by body surface area (BSA).

Doppler signal recorded at LV outflow tract (LVOT) from the apical window was used to measure peak LVOT velocity and its velocity time integral (VTI). Stroke volume was calculated from the pulsed wave Doppler velocity profile and the cross-sectional area at the LVOT. Transmitral blood inflow Doppler signals were used to measure peak early (E) and late (A) diastolic velocities, and their VTIs. From the pulsed wave Tissue Doppler Imaging (TDI) recordings, we measured peak early (e′) and late (a′) diastolic mitral annular velocities at the 4 acquisition sites (septal, lateral, inferior, and posterior).

SphygmoCor measurements

The complete protocol for arterial measurements is provided in the Data Supplement. Briefly, all arterial measurements were obtained by an experienced observer,[18] after the participant rested in the supine position for at least 15 minutes. During 8 seconds, the carotid and femoral arterial waveforms were recorded consequently by applanation tonometry, using a high-fidelity SPC-301 micromanometer (Millar Instruments, Inc., Houston, TX) interfaced with a computer running the SphygmoCor software version 8.2 (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). To calibrate the pulse wave, brachial BP was recorded immediately before the tonometric recordings. We used the carotid pressure waveform to derive central hemodynamic parameters. The software returns the central systolic BP and the pressure at the first (P1) and second (P2) peak or shoulder of the carotid waveform. Pulse pressure was defined as the difference between central systolic and diastolic BP. Mean arterial BP was calculated as diastolic BP plus one third of pulse pressure. Augmentation pressure was the difference between P2 and P1. Aortic pulse wave velocity (PWV) was measured by sequential recordings of

the arterial pressure wave at the carotid and femoral arteries as previously described.[18] Aortic PWV was calculated as the ratio of the pulse wave distance (in meters) to the transit time (in seconds).

Other measurements

Detailed information on other measurements is given in the online Data Supplement Methods section. Venous blood samples were drawn after overnight fasting, in which hemoglobin, hematocrit, blood glucose, total cholesterol, serum sodium, serum potassium, serum uric acid, and serum creatinine were determined by standard clinical laboratory methods. Estimated glomerular filtration rate was calculated using the MDRD formula.[19]

Statistical methods

For database management and statistical analysis, we used SAS software version 9.3 (SAS Institute, Cary, NC). Normality was evaluated by computation of skewness and kurtosis coefficients. The central tendency and the

Table 1. Clinical characteristics of study participants

Characteristics	Men (n = 88)	Women (n = 83)	*P* value
Anthropometrics			
Age, years	52.8 ± 14.0	52.0 ± 14.0	0.71
Height, cm	176.2 ± 7.4	164.0 ± 6.9	<0.0001
Weight, kg	85.1 ± 15.5	72.7 ± 14.1	<0.0001
Body mass index, kg/m^2	27.4 ± 3.7	27.0 ± 4.9	0.60
Systolic BP[a], mm Hg	128 ± 14	126 ± 17	0.29
Diastolic BP[a], mm Hg	80 ± 9	79 ± 9	0.83
Pulse pressure[a], mm Hg	49 ± 9	46 ± 11	0.15
Mean arterial pressure[a], mm Hg	96 ± 10	95 ± 11	0.52
Heart rate[a], beats/min	59 ± 9	62 ± 9	0.14
Questionnaire data			
Current smoking, n (%)	17 (19.3)	11 (13.3)	0.31
Alcohol use, n (%)	45 (51.1)	15 (18.1)	<0.0001
Treated for hypertension, n (%)	31 (35.2)	19 (22.9)	0.09
β-blockers, n (%)	18 (20.5)	7 (8.4)	0.03
Diuretics, n (%)	11 (12.5)	9 (10.8)	0.74
CCB, n (%)	9 (10.2)	3 (3.6)	0.09
ACE or ARB, n (%)	8 (9.1)	9 (10.8)	0.70
Cardiac disease[b], n (%)	8 (9.1)	1 (1.2)	0.04
Renal dysfunction, n (%)	6 (6.8)	2 (2.4)	0.17
Diabetes, n (%)	3 (3.4)	4 (4.8)	0.71
Biochemical data			
Hematocrit, %	42.7 ± 2.8	40.2 ± 2.8	<0.0001
Blood glucose, mmol/L	4.94 ± 0.65	4.71 ± 0.47	0.008
Total cholesterol, mmol/L	4.76 ± 0.83	5.16 ± 0.84	0.002
Serum sodium, mmol/L	140.1 ± 2.4	140.2 ± 1.8	0.78
Serum potassium, mmol/L	4.57 ± 0.42	4.46 ± 0.35	0.07
Serum uric acid, μmol/L	363.8 ± 66.1	273.2 ± 71.7	<0.0001
Serum creatinine, μmol/L	81.8 (69.0–102.5)	63.7 (53.9–77.8)	<0.0001
eGFR, ml/min per 1.73 m^2	90.1 ± 18.7	93.2 ± 16.3	0.25

Values are mean ± SD or number of subjects (%) or median (10%–90% percentile). *P* values are for the differences between men and women.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BP, blood pressure; CCB, calcium channel blockers; eGFR, estimated glomerular filtration rate.

[a]Blood pressure and heart rate were measured after echocardiographic examination in supine position.

[b]Cardiac disease included symptomatic heart failure (n = 2) and coronary heart disease (n = 7).

spread of the data are reported as mean ± SD or as median and 10%–90% percentiles. We compared means, medians, and proportions by means of the 2-sample *t*-test, the Wilcoxon rank-sum test, and the chi-square test, respectively. Significance was $P < 0.05$ on 2-sided test. We searched for variables associated with RRI measured on a continuous scale using stepwise linear regression. The anthropometrics and hemodynamic variables considered for entry in the models were sex, age, body height, body weight, waist circumference, body mass index, heart rate, systolic and diastolic BP, pulse pressure, mean arterial pressure, total cholesterol, serum uric acid, serum creatinine, estimated glomerular filtration rate, kidney length, current smoking and drinking, and class of antihypertensive drug treatment (diuretics, renin–angiotensin system blockers, β-blockers, and calcium channel blockers). *P* values for independent variables to enter and to stay in the models were set at 0.05. We ran regression diagnostics to exclude possible collinearity, which affects the stability and inflates the standard errors of the regression parameters. We used multiple linear regression analysis to investigate the associations between RRI and explanatory variables, while adjusting for covariables identified in stepwise linear regression. We expressed multivariable-adjusted effect sizes for a 1-SD increase in the explanatory variables.

Table 2. Central hemodynamics, arterial, echocardiographic, and renal characteristics of study participants

Characteristics	Men (n = 88)	Women (n = 83)	*P* value
SphygmoCor measurements			
Central hemodynamics[a]			
Systolic blood pressure, mm Hg	124 ± 14	126 ± 20	0.58
Pulse pressure, mm Hg	42 ± 12	46 ± 16	0.19
Augmentation pressure, mm Hg	12 ± 8	16 ± 10	0.004
Pulse wave velocity, m/s	7.81 ± 1.59	7.40 ± 1.59	0.12
Echocardiographic structural indexes			
Left atrial volume index, ml/m^2	26.2 ± 7.1	23.6 ± 5.9	0.01
LV end-diastolic internal diameter, cm	5.21 ± 0.36	4.77 ± 0.37	<0.0001
Posterior end-diastolic wall thickness, cm	1.03 ± 0.13	0.91 ± 0.11	<0.0001
Interventricular wall thickness, cm	1.10 ± 0.18	0.96 ± 0.15	<0.0001
LV mass index, g/m^2	106.1 ± 23.0	87.5 ± 19.3	<0.0001
LV outflow diameter, cm	2.25 ± 0.17	2.03 ± 0.15	<0.0001
Doppler volume indexes			
LVOT peak velocity, cm/s	1.10 ± 0.17	1.10 ± 0.17	0.78
LVOT VTI , cm	22.3 ± 3.50	23.0 ± 3.81	0.23
LVOT stroke volume, ml	88.7 ± 18.6	74.7 ± 16.9	<0.0001
E peak, cm/s	65.0 ± 16.5	72.5 ± 16.6	0.004
E VTI, cm	9.16 ± 2.12	9.67 ± 2.11	0.11
A peak, cm/s	55.5 ± 13.2	64.0 ± 16.0	0.0002
A VTI, cm	4.77 ± 1.31	5.38 ± 1.53	0.006
E/A ratio	1.25 ± 0.50	1.23 ± 0.52	0.79
TDI indexes			
e′ peak[b], cm/s	10.1 ± 3.6	10.3 ± 3.6	0.71
a′ peak[b], cm/s	9.7 ± 2.1	9.3 ± 1.9	0.24
E/e′ ratio	6.94 ± 2.29	7.64 ± 2.36	0.05
Renal ultrasound			
Renal length, cm	11.2 ± 0.63	10.6 ± 0.77	<0.0001
RRI	0.585 ± 0.059	0.612 ± 0.056	0.002

Values are mean ± SD. *P* values are for the differences between men and women.

Abbreviations: BP, blood pressure; LV, left ventricular; LVOT left ventricular outflow tract; RRI, renal resistive index; TDI, tissue Doppler imaging; VTI, velocity time integral.

[a]Measurements of central hemodynamics were available for 120 participants.

[b]Averaged of septum, lateral, inferior and posterior mitral annulus sites.

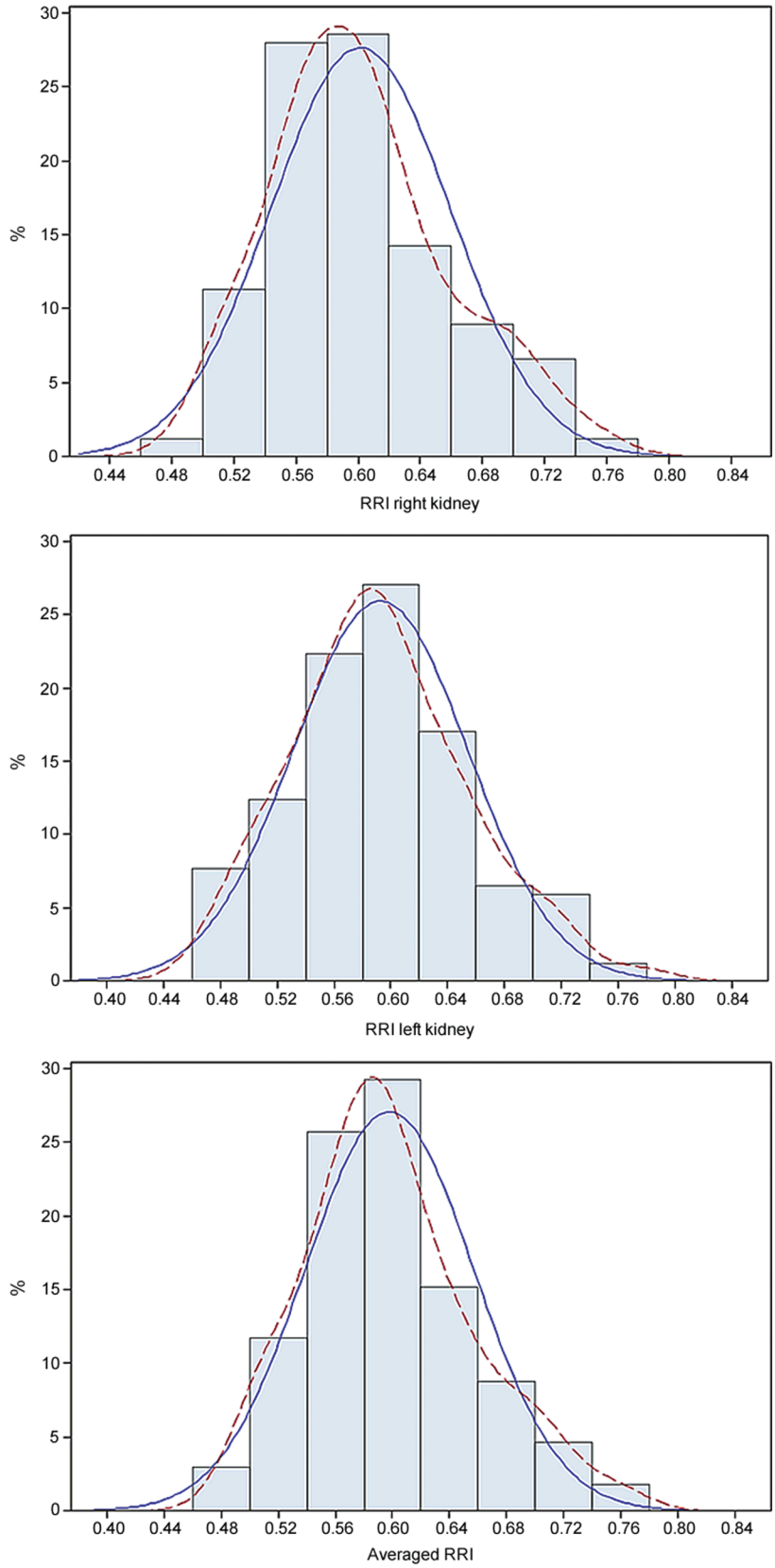

Figure 1. The histograms of renal resistive index (RRI) of right, left, and both kidneys in the entire population. The curves represent the fitted normal (full line) and Kernel (dotted line) density plots.

Table 3. Correlates of the averaged RRI in stepwise regression

	RRI			
Parameter	**Partial R^2 (%)**	**β ± SE**	**95% CI**	***P* value**
Age (+10 years)	38.8	0.015 ± 0.003	0.009 to 0.020	<0.0001
Being female	8.3	0.025 ± 0.007	0.011 to 0.040	<0.0001
Body height (+10 cm)	3.9	−0.021 ± 0.005	−0.031 to −0.012	<0.0001
Body weight (+10 kg)	1.6	0.011 ± 0.002	0.006 to 0.016	0.0073
Pulse pressure (+10 mm Hg)	8.7	0.035 ± 0.004	0.028 to 0.042	<0.0001
Mean arterial pressure (+10 mm Hg)	5.0	−0.022 ± 0.003	−0.029 to −0.016	<0.0001
Use of β-blockers	2.8	0.025 ± 0.008	0.009 to 0.040	0.0005
Total adjusted R^2	67.6			

The covariables considered for entry into the stepwise regression model were sex, age, body height, body weight, waist circumference, body mass index, heart rate, systolic and diastolic blood pressure, pulse pressure, mean arterial pressure, total cholesterol, serum uric acid, serum creatinine, eGFR, kidney length, current smoking and drinking, and class of antihypertensive drug treatment (diuretics, renin–angiotensin system blockers, β-blockers, and calcium channel blockers). We set the *P* values for covariables to enter and to stay in the regression models at 0.05. Values are mutually adjusted partial regression coefficients ± SE, 95% confidence intervals, and *P* values. Variance inflation factors (VIF) were ≤2.00 for all explanatory variables with exception of VIF for body height (VIF = 2.85).

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; RRI, renal resistive index.

RESULTS

Characteristics of the participants

The 171 participants included 83 (48.5%) women and 88 (51.5%) hypertensive participants of whom 50 (29.2%) were on antihypertensive drug treatment. Mean age was 52.2 ± 14.0 years. In our study, 50 (29.2%) participants were on one or more antihypertensive drugs (β-blockers, 25 patients; diuretics, 20 patients; calcium channel blockers, 12 patients; ACE inhibitors or angiotensin receptor blockers, 17 patients). Table 1 lists the clinical and biochemical characteristics of the participants by sex. Men had higher body height, body weight, alcohol use, β-blockers use, and prevalence of cardiac disease compared to women (Table 1). Overall, 7 subjects (4.1%) had renal insufficiency (estimated glomerular filtration rate < 60 ml/min per 1.73 m^2). Hematocrit, blood glucose, serum uric acid, and serum creatinine were higher in men than in women (Table 1). Table 2 presents the hemodynamic, arterial, and echocardiographic characteristics of the participants by sex. In this cohort, women had higher central augmentation pressure than men (Table 2). All echocardiographic structural measurements were greater in men than in women (Table 2). Men had higher LV outflow stroke volume than women, whereas women had higher transmitral Doppler diastolic flow velocities (E and A velocity peaks and A VTI) compared to men (Table 2).

RRI and its determinants

Figure 1 shows the distribution of RRI of left and right kidney and the RRI averaged for both kidneys. The distributions of RRI were positively skewed ($P \leq 0.01$) with the coefficients of skewness ranging between 0.41 and 0.54 (Figure 1). In the entire population, mean RRI was 0.59 ± 0.062, 0.60 ± 0.058, and 0.60 ± 0.059 for left, right, and for both kidneys, respectively. For the further statistical analyses, we averaged the RRI measurements of left and right kidneys. Renal length was greater in men than in women, whereas women had higher RRI (Table 2).

Supplementary Tables S1 and S2 list the characteristics of participants by tertiles of the distribution of RRI. In an univariate analysis, the averaged RRI correlated significantly with age, body height, systolic BP, and pulse pressure (Supplementary Figure S2). In stepwise regression analysis, RRI independently and significantly increased with age, female sex, body weight, and peripheral pulse pressure, whereas averaged RRI decreased with body height and mean arterial pressure (Table 3). We also noticed that, after adjustment, RRI was higher in participants treated with β-blockers (Table 3). The covariables in the final model explained 67.6% of the total variance of RRI. Most of the total variance of RRI was explained by age (38.8%).

Relation of RRI with central hemodynamics and arterial characteristics

Table 4 presents the relationship of RRI with central hemodynamics and arterial characteristics, while accounting for age, sex, body height, body weight, and use of β-blockers. In an adjusted model with central systolic BP as the explanatory variable, we introduced diastolic BP as an additional covariable. In model with central pulse pressure as the explanatory variable, we entered mean arterial pressure as an additional covariable. We observed significant and positive correlations of RRI with central systolic BP ($P = 0.021$) and central pulse pressure ($P < 0.0001$) (Table 4). For a 1-SD increase in central systolic BP and central pulse pressure, RRI increased by 0.010 and 0.029, respectively. Central systolic BP and central pulse pressure explained 5.0% and 14.4% of the variances in the RRI, respectively, that was not yet explained by other covariables.

Table 4. Multivariable-adjusted correlations of RRI with central blood pressure, arterial characteristics, and echocardiographic indexes

	RRI		
Explanatory variables	**Effect size**	**95% CI**	***P* value**
Central blood pressure and arterial characteristics			
Central systolic blood pressure (+17 mm Hg)	0.010	0.0016 to 0.019	0.021
Central pulse pressure (+15 mm Hg)	0.029	0.020 to 0.037	<0.0001
Augmentation pressure (+9 mm Hg)	−0.0039	−0.030 to 0.017	0.59
Pulse wave velocity (+1.6 m/s)	0.0069	−0.0017 to 0.015	0.12
Echocardiographic structural indexes			
Left atrial volume index (+6.7 ml/m^2)	0.0048	−0.0018 to 0.012	0.15
LV end-diastolic internal diameter (+0.43 cm)	−0.0022	−0.0091 to 0.0047	0.53
Posterior end-diastolic wall thickness (+0.14 cm)	−0.0043	−0.012 to 0.0033	0.87
Interventricular wall thickness (+0.18 cm)	0.0006	−0.0065 to 0.0077	0.43
LV mass index (+23 ml/m^2)	−0.0028	−0.0093 to 0.0037	0.40
Doppler indexes			
LV outflow			
LVOT peak velocity (+17 cm/s)	0.0065	0.0015 to 0.011	0.012
LVOT VTI (+3.7 cm)	0.0088	0.0037 to 0.014	0.0008
LVOT stroke volume (+19 ml)	0.0071	0.0010 to 0.013	0.023
Transmitral diastolic inflow			
E peak velocity (+17 cm/s)	0.0097	0.0034 to 0.016	0.0027
E VTI (+2.1 cm)	0.0077	0.0017 to 0.013	0.010
A peak velocity (+15 cm/s)	−0.0021	−0.0093 to 0.0051	0.58
A VTI (+1.5 cm)	−0.0007	−0.0081 to 0.0067	0.85
E/A ratio (+0.51)	0.013	0.0046 to 0.020	0.0017
TDI indexes			
e′ peak velocity (+3.6 cm/s)	0.0086	−0.0014 to 0.018	0.10
a′ peak velocity (+2.0 cm/s)	−0.0044	−0.010 to 0.0016	0.15
E/e′ ratio (+2.4)	0.0053	−0.0017 to 0.012	0.14

Effect sizes and corresponding 95% CI are expressed for a 1-SD increase in the explanatory variables and were adjusted for age, sex, body height, body weight, and use of β-blockers. For central systolic blood pressure, adjusted model included diastolic blood pressure. For central pulse pressure, adjusted model included mean arterial pressure. For augmentation pressure and pulse wave velocity, adjusted models included both mean arterial pressure and central pulse pressure. For echocardiographic indexes, adjusted model included mean arterial pressure and brachial pulse pressure.

Abbreviations: CI, confidence interval; LV, left ventricular; LVOT, left ventricular outflow tract; RRI, renal resistive index; TDI, tissue Doppler imaging; VTI, velocity time integral.

Figure 2 shows the correlations between the adjusted RRI and the adjusted central systolic BP and central pulse pressure ($P < 0.0001$).

While adjusting for the important covariables including central pulse pressure and mean arterial pressure, we did not observe any significant association between RRI and arterial characteristics such as augmentation pressure and aortic PWV (Table 4).

Relation of RRI with echocardiographic parameters

Table 4 lists the relationship between RRI and echocardiographic indexes, while accounting for age, sex, body height, body weight, pulse pressure, mean arterial pressure, and use of β-blockers. RRI was not associated with any of the echocardiographic indexes reflecting LV structure ($P \geq 0.40$) (Table 4). We observed significant and independent associations between RRI and Doppler indexes characterizing blood flow during systole such as LVOT peak velocity, LVOT VTI, and LV stroke volume (Table 4). For a 1-SD increase in LVOT peak velocity, LVOT VTI, and LV stroke volume, RRI increased by 0.0065, 0.0088, and 0.0071, respectively. Furthermore, RRI was directly and significantly associated with transmitral Doppler diastolic indexes such as E velocity, E VTI, and E/A ratio ($P \leq 0.0027$) (Table 4). For a 1-SD increase in E peak, E VTI, and E/A, RRI increased by 0.0097,

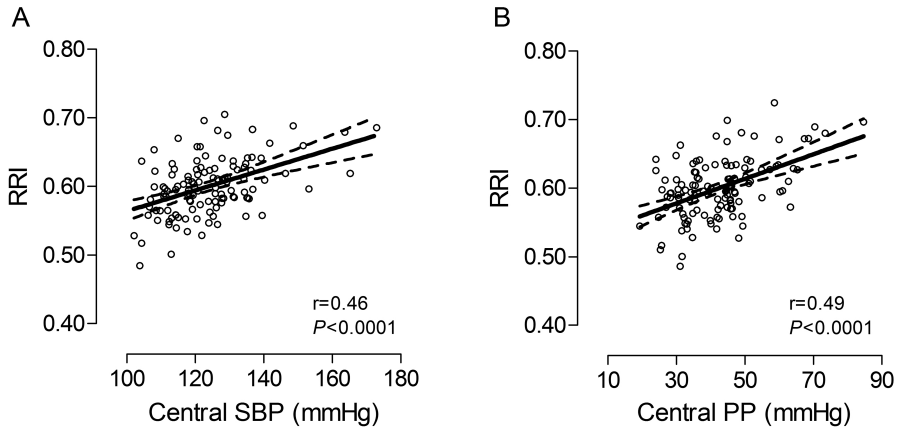

Figure 2. Scatter plots of renal resistive index (RRI) vs. central systolic blood pressure (SBP; panel **A**) and central pulse pressure (PP; panel **B**) in multivariable-adjusted analyses. The full and dotted lines represent the regression line and the 95% confidence interval, respectively. The regression slopes were standardized to the distribution in all 120 subjects with available central hemodynamics (mean and ratio) of age, sex, and anthropometric characteristics.

0.0077, and 0.013, respectively (Table 4). We repeated our analyses after exclusion of subjects on antihypertensive drugs. In 121 untreated subjects, our findings remained consistent (Supplementary Table S3).

The adjusted RRI significantly correlated with the adjusted LVOT peak velocity (r = 0.19) and LVOT VTI (r = 0.23) (Figure 3). Moreover, significant correlations were observed between the adjusted RRI and diastolic Doppler indexes with Pearson coefficients ranging between 0.17 and 0.22 (Figure 3).

DISCUSSION

The key finding of this study was that RRI was significantly and independently associated with central pulse pressure and intracardiac Doppler blood flow indexes. In our population study, for the first time, we described the relation between renal and cardiac Doppler blood flow waveforms. Furthermore, in our study, we reported other anthropometric and hemodynamic determinants of RRI that are in line with previous reports in the general population,[11] hypertensive patients,[14] and renal allograft recipients.[5] In particular, we found that in our cohort, RRI significantly and independently increased with female sex, age, peripheral pulse pressure, and body weight and decreased with body height and mean arterial pressure. Moreover, RRI significantly and independently increased with use of β-blockers.

Previous studies showed that the Doppler arterial waveform signal obtained in the intrarenal arteries is the product of a complex interaction between a number of factors such as systemic hemodynamics and peripheral vascular resistance and compliance.[3] Indeed, experimental studies demonstrated that impaired renal vascular compliance and increased pulse pressure lead to significant changes in RRI of isolated perfused rabbit kidneys.[20,21]

Peripheral arterial resistance is a main determinant of mean arterial pressure and depends on the physical characteristics of the arterial tree. On the other hand, the pulsatile component, represented by pulse pressure, depends on compliance of aorta and large arteries. The aortic walls elastically expand to accommodate the ejected blood during systole and, therefore, dampen pulsatility and maintains a continuous blood flow from the heart to the periphery. With aging, the rigidity is more pronounced in the aorta than in peripheral conduit arteries, leading to less protection of the microcirculation from high-pressure transmission in organs with high resting flow, such as the kidneys.[22] In fact, increased pulsatile stress leads to tearing of endothelial and smooth muscle cells of small arteries in kidney.[23] Along these lines, several studies have shown that pulse pressure is an independent prognostic factor for cardiovascular mortality and morbidity in patients with chronic kidney disease[24] and in renal transplant patients.[25]

To our knowledge, only 2 previous reports in hypertensive patients[26,27] addressed the associations of RRI with central pulse pressure and arterial stiffness. In keeping with our observations, these studies[26,27] demonstrated significant association between RRI and aortic pulse pressure independent of other covariables. Similar to our findings, no significant associations were observed with arterial stiffness indexes such as augmentation pressure and carotid–femoral pulse wave velocity after adjustment for important covariables including age.[26,27]

In addition to vascular properties and central pulse pressure, another important factor influencing the Doppler-based RRI is renal blood flow.[28] The kidney is one of the peripheral territories with the highest perfusion because of its pivotal role in the metabolic balance. In fact, kidneys receive approximately 15%–25% of total cardiac output via renal arteries depending on the state of body and the volume of blood that the LV ejects. Using Doppler echocardiography, we could also quantify intracardiac blood flows through quantification of blood velocities during systole and diastole.[29] Previous studies showed that changes in the total circulating volume (preload) significantly influenced Doppler blood flow velocity profiles.[30,31]

So far, only 1 study[32] in 99 patients with treated essential hypertension investigated the relationship between RRI and the velocity ratio of atrial filling to early diastolic LV filling (A/E ratio). However, in this study, the authors

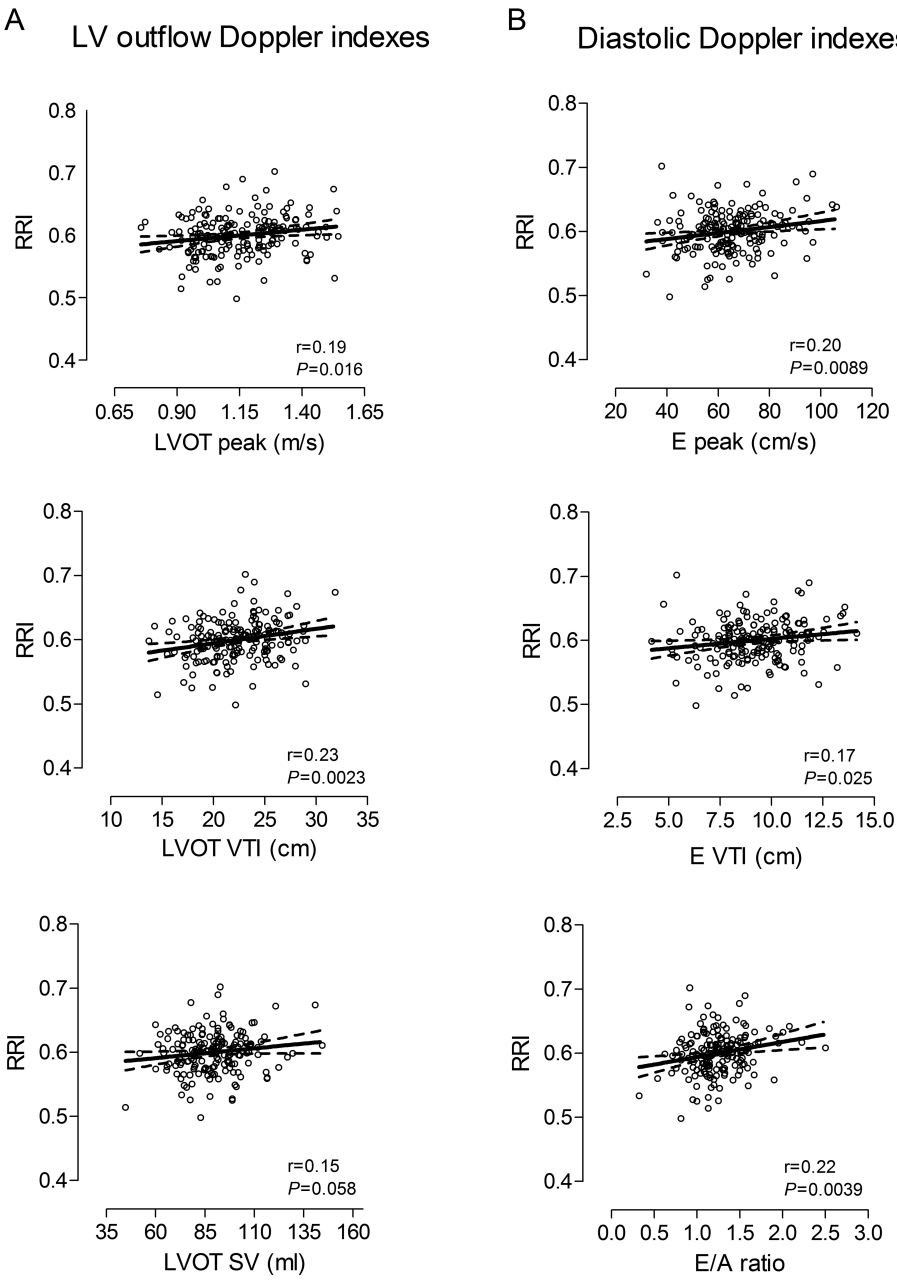

Figure 3. Scatter plots of renal resistive index (RRI) vs. left ventricular outflow tract (LVOT) systolic (panel **A**) and transmitral diastolic (panel **B**) Doppler flow indexes in multivariable-adjusted analyses. The full and dotted lines represent the regression line and the 95% confidence interval, respectively. The regression slopes were standardized to the distribution in all 171 subjects (mean and ratio) of age, sex, and anthropometric and hemodynamic characteristics. Abbreviations: SV, stroke volume; VTI, velocity time integral.

did not observe an independent association between RRI and LV transmitral A/E ratio.[32] Moreover, the authors did not investigate associations between RRI and peak early LV diastolic flow velocity or LV peak systolic velocity and their VTIs.[32] Thus, to our knowledge, our study was the first to assess in a general population the correlation between RRI and Doppler indexes of LV peak systolic and diastolic blood flow velocities. With adjustments applied, we demonstrated in continuous analyses that RRI significantly increased with systolic and early diastolic intracardiac Doppler blood flow. Our findings imply that exposure of small renal arteries to high blood flow in addition to high pulsatile pressure leads to increased RRI and might in long run result to microvascular damage and, therefore, renal insufficiency.[23] Along these lines, recent study in hypertensive patients[33] demonstrated that impairment of renal hemodynamics as assessed by increased RRI was associated with an increased risk of cardiovascular and renal outcomes.

The present study must be interpreted within the context of its potential limitations. First, echocardiographic measurements are prone to measurements errors due to bad visualization, signal noise, and acoustic artifacts. In the present study,

only 1 experienced observer recorded all cardiac and renal ultrasound images for off-line analyses. Furthermore, digitally stored renal images were centrally post-processed using dedicated software by 2 observers in duplicate. Second, our sample size was smaller than in published studies in general population[11] or in hypertensive patients.[12–14] We, therefore, could not rule out that the associations of RRI with some indexes reflecting arterial stiffness and LV structure that failed to reach statistical significance were due to a type II error. However, the research question addressed in this study and our conclusions were expanding the findings of previous publications.[11–14] Third, the cross-sectional design of the study does not allow for a causal interpretation of the relationships found.

In conclusion, we demonstrated that in unselected subjects, RRI was significantly associated with central pulse pressure and LV systolic and diastolic Doppler blood flow indexes. Our findings imply that the interaction between the heart and peripheral circulation in the kidney is a complex physiological phenomenon. In addition to renal vascular properties, the anthropometric and cardiac hemodynamic factors influenced the intrarenal arterial Doppler waveform patterns. Further longitudinal population studies are required to clarify whether early detection of Doppler changes in intrarenal arteries might yield an improvement in the adverse cardiovascular and renal outcome in general population.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. Iyngkaran P, Schneider H, Devarajan P, Anaverka N, Krum H, Ronco C. Cardio-renal syndrome: new perspective in diagnostics. *Semin Nephrol* 2012; 32:3–17.
2. Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. *Circulation* 2010; 121:2592–2600.
3. Tublin ME, Bude RO, Platt JF. The resistive index in renal doppler sonography: where do we stand? *Am J Roentgenol* 2003; 180:885–892.
4. Radermacher J, Mengel M, Ellis S, Stuht S, Hiss M, Schwarz A, Eisenberger U, Burg M, Luft FC, Gwinner W, Haller H. The renal arterial resistance index and renal allograft survival. *N Engl J Med* 2003; 349:115–124.
5. Naesens M, Heylen L, Lerut E, Claes K, De Wever L, Claus F, Oyen R, Kuypers D, Evenepoel P, Bammens B, Sprangers B, Meijers B, Pirenne J, Monbaliu D, de Jonge H, Metalidis C, De Vusser K, Vanrenterghem Y. Intrarenal resistive index after renal transplantation. *N Engl J Med* 2013; 369:1797–1806.
6. Radermacher J, Chavan A, Bleck J, Vitzhum A, Stoess B, Gebel MJ, Galanski M, Koch KM, Haller H. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med* 2001; 344:410–417.
7. Crutchley TA, Pearce JD, Craven TE, Stafford JM, Edwards MS, Hansen KJ. Clinical utility of the resistive index in atherosclerotic renovascular disease. *J Vasc Surg* 2009; 49:148–155.
8. Radermacher J, Ellis S, Haller H. Renal resistance index and progression of renal disease. *Hypertension* 2002; 39:699–703.
9. Le Dorze M, Bouglé A, Deruddre S, Duranteau J. Renal Doppler ultrasound: a new tool to assess renal perfusion in critical illness. *Shock* 2012; 37:360–365.
10. Darmon M, Schortgen F, Vargas F, Liazydi A, Schlemmer B, Brun-Buisson C, Brochard L. Diagnostic accuracy of Doppler renal resistive index for reversibility of acute kidney injury in critically ill patients. *Intensive Care Med* 2011; 37:68–76.
11. Ponte B, Pruijm M, Ackermann D, Vuistiner P, Eisenberger U, Guessous I, Rousson V, Mohaupt MG, Alwan H, Ehret G, Pechere-Bertschi A, Paccaud F, Staessen JA, Vogt B, Burnier M, Martin PY, Bochud M. References values and factors associated with renal resistive index in a family-based population study. *Hypertension* 2014; 63:136–142.
12. Tedesco MA, Natale F, Mocerino R, Tassinario G, Calabrò R. Renal resistive index and cardiovascular organ damage in a large population of hypertensive patients. *J Hum Hypertens* 2003; 21:291–296.
13. Pontremoli R, Viazzi F, Martinoli C, Ravera M, Nicolella C, Berruti V, Leoncini G, Ruello N, Zagami P, Bezante GP, Derchi LE, Deferrari G. Increased renal resistive index in patients with essential hypertension: a marker of target organ damage. *Nephrol Dial Transplant* 1999; 14:360–365.
14. Doi Y, Iwashima Y, Yoshihara F, Kamide K, Takata H, Fujii T, Kubota Y, Nakamura S, Horio T, Kawano Y. Association of renal resistive index with target organ damage in essential hypertension. *Am J Hypertens* 2012; 25:1292–1298.
15. Pruijm M, Ponte B, Ackermann D, Vuistiner P, Paccaud F, Guessous I, Ehret G, Eisenberger U, Mohaupt M, Burnier M, Martin PY, Bochud M. Heritability, determinants and reference values of renal length: a family-based population study. *Eur Radiol* 2013; 23:2899–2905.
16. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307–310.
17. Gottdiener JS, Bednarz J, Devereux R, Gardin J, Klein A, Manning WJ, Morehead A, Kitzman D, Oh J, Quinones M, Schiller NB, Stein JH, Weissman NJ; American Society of Echocardiography. American Society of Echocardiography recommendations for use of echocardiography in clinical trials. *J Am Soc Echocardiogr* 2004; 17:1086–1119.
18. Liu YP, Thijs L, Kuznetsova T, Gu YM, Asayama K, Stolarz-Skrzypek K, Jin Y, Verhamme P, Struijker-Boudier HA, Staessen JA. Central systolic augmentation indexes and urinary sodium in a white population. *Am J Hypertens* 2013;26:95–103.
19. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Ann Intern Med* 2003; 139:137–147.
20. Murphy ME, Tublin ME. Understanding the Doppler RI: impact of renal arterial distensibility on the RI in a hydronephrotic ex vivo rabbit kidney model. *J Ultrasound Med* 2000; 19:303–314.
21. Tublin ME, Tessler FN, Murphy ME. Correlation between renal vascular resistance, pulse pressure and the resistive index in isolated perfused rabbit kidneys. *Radiology* 1999; 213:258–264.

22. Briet M, Boutouyrie P, Laurent S, London GM. Arterial stiffness and pulse pressure in CKD and ESRD. *Kidney Int* 2012; 82:388–400.
23. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension* 2005; 46:200–204.
24. Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM, London GM. Central pulse pressure and mortality in end-stage renal disease. *Hypertension* 2002; 39:735–738.
25. Fernández-Fresnedo G, Escallada R, Martin de Francisco AL, Ruiz JC, Rodrigo E, Sanz de Castro S, González Cotorruelo J, Arias M. Association between pulse pressure and cardiovascular disease in renal transplant patients. *Am J Transplant* 2005; 5:394–398.
26. Hashimoto J, Ito S. Central pulse pressure and aortic stiffness determine renal hemodynamics: pathophysiological implication for microalbuminuria in hypertension. *Hypertension* 2011; 58:839–846.
27. Stea F, Sgrò M, Faita F, Bruno RM, Cartoni G, Armenia S, Taddei S, Ghiadoni L. Relationship between wave reflection and renal damage in hypertensive patients: a retrospective analysis. *J Hypertens* 2013; 31:2418–2424.
28. Darmon M, Schnell D, Zeni F. Doppler-based renal resistive index: a comprehensive review. In Vincent J (ed), *Yearbook of Intensive Care and Emergency Medicine*. Springer: Heidelberg, 2010, pp. 331–338.
29. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Sociaty of Echocardiography. *J Am Soc Echocardiogr* 2002; 15:167–184.
30. Mendes L, Ribeiras R, Adragão T, Lima S, Horta E, Reis C, Amaral T, Aguiar C, Gouveia R, Silva A. Load-independent parameters of diastolic and systolic function by speckle tracking and tissue doppler in hemodialysis patients. *Rev Port Cardiol* 2008; 27:1011–1025.
31. Hung KC, Huang HL, Chu CM, Yeh KH, Fang JT, Lin FC. Effects of altered volume loading on left ventricular hemodynamics and diastolic filling during hemodialysis. *Ren Fail* 2004; 26:141–147.
32. Ogata C, Horio T, Kamide K, Takiuchi S, Kawano Y. Association between left ventriculardiastolic dysfunction and renal hemodynamic change in patients with treated essential hypertension. *Hypertens Res* 2003; 26:971–978.
33. Doi Y, Iwashima Y, Yoshihara F, Kamide K, Hayashi S, Kubota Y, Nakamura S, Horio T, Kawano Y. Renal resistive index and cardiovascular and renal outcomes in essential hypertension. *Hypertension* 2012; 60:770–777.

American Journal of Hypertension 2014

Doppler indexes of left ventricular systolic and diastolic flow and central pulse pressure in relation to renal resistive index

Short title: RRI and cardiac hemodynamics

Supplemental Material

Supplemental Methods

Study Design

This study is nested in the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO), a large family-based population resource on the genetic epidemiology of cardiovascular phenotypes, for which recruitment started in 1985 and continued through 2010. The FLEMENGHO study consists of a random population sample stratified by sex and age from a geographically defined area in northern Belgium. The initial participation rate was 78.0% (1). Seven Belgian municipalities provided listings of all inhabitants sorted by address. Households, subjects living at the same address, were the sampling unit. They were numbered consecutively and a random number list was generated by a SAS randomisation function (SAS Institute, Car, NC). Households with a list matching number were invited. The Ethics Committee of the University of Leuven approved the study and participants provided informed consent.

Echocardiography

The participants refrained from smoking, heavy exercise, and drinking alcohol or caffeine-containing beverages for at least 3 hours before echocardiography. The blood pressure during echocardiography was the average of two readings, obtained with a validated OMRON 705IT device (Omron Corp., Tokyo, Japan) at the end of the echocardiographic examination.

Data Acquisition

One experienced physician (T.K.) did the ultrasound examination, using a Vivid E9 (GE Vingmed, Horten, Norway) interfaced with a 2.5- to 3.5-MHz phased-array probe, according to the recommendations of the American Society of Echocardiography (2). With the subjects in partial left decubitus and breathing normally, the observer obtained images, together with

a simultaneous ECG signal, along the parasternal long and short axes and from the apical 4- and 2 chamber long-axis views. All recordings included at least 5 cardiac cycles and were digitally stored for off-line analysis. M-mode echocardiograms of the LV were recorded from the parasternal long-axis view under control of the two-dimensional image. The ultrasound beam was positioned just below the mitral valve at the level of the posterior chordae tendineae. To record pulsed-wave Doppler LV outflow and mitral inflow velocities from the apical window, the observer positioned the Doppler sample volume in the LV outflow tract (LVOT) and at the mitral valve tips, respectively.

Using TDI (Tissue Doppler Imaging), the observer recorded low-velocity, high-intensity myocardial signals at a high frame rate (>190 FPS), while adjusting the imaging angle to ensure a parallel alignment of the ultrasound beam with the myocardial segment of interest. From the apical window, the sonographer placed a 5-mm Doppler sample at the septal, lateral, inferior and posterior sites of the mitral annulus.

Off-Line Analysis

One experienced physician (T.K.) analyzed digitally stored images, averaging 3 heart cycles for statistical analysis, using a workstation running the EchoPac, version 112 software package (GE Vingmed, Horten, Norway). The LV internal diameter and interventricular septal and posterior wall thickness were measured at end-diastole from the 2 dimensionally guided M-mode tracing according to guidelines (2). When optimal orientation of M-mode ultrasound beam could not be obtained, the reader performed linear measurements on correctly oriented two-dimensional images. End-diastolic LV dimensions were used to calculate LV mass by an anatomically validated formula (3). LV mass index (LVMI) was LV mass divided by body surface area (BSA), calculated as body weight$^{0.425}$ (in kg) x body height$^{0.725}$ (in cm) x 0.007184. We measured left atrial (LA) dimensions in 3 orthogonal

planes: the parasternal long, lateral, and supero-inferior axes. LA volume was calculated using the prolate-elipsoid method and was indexed to BSA (4).

Doppler signal recorded at the LVOT was used to measure peak LVOT velocity and its velocity time integral (VTI). Stroke volume was calculated from the pulsed-wave Doppler velocity profile and the cross sectional area at the LVOT. From the transmitral flow signal, we measured peak early diastolic velocity (E), peak late diastolic velocity (A), and their VTIs. From the TDI recordings, we measured peak early (e') and late (a') diastolic mitral annular velocities at the 4 acquisition sites (septal, lateral, inferior, and posterior).

Reproducibility

To determine intra-observer reproducibility, the experienced echocardiographists (T.K.) analyzed the echocardiograms of 17 subjects twice. Intra-observer reproducibility coefficient of a measurement was the 2SD interval about the mean of the relative differences across pairwise readings. The intra-observer reproducibility was 2.2% for LV internal end-diastolic diameter, 4.6% for LV wall thickness, 4.3% for LV mass. For conventional Doppler parameters, the reproducibility was 5.0% for transmitral E peak, 6.6% for transmitral A peak, 6.3% for LVOT peak velocity and 6.4% for LVOT VTI. For tissue Doppler velocities, as reported previously, the reproducibility across the four sampling sites ranged from 4.5% to 5.3% for e' velocities and from 4.0% to 4.5% for a' velocities.

SphygmoCor Measurements

All arterial measurements were obtained by an experienced observer according standardized protocol (5), after the participant rested in the supine position for at least 15 min. During 8 seconds, the carotid and femoral arterial waveforms were recorded consequently by applanation tonometry, using a high-fidelity SPC-301 micromanometer (Millar Instruments, Inc., Houston, TX, USA) interfaced with a computer running the SphygmoCor software version 8.2 (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). Recordings

were discarded if systolic or diastolic variability of consecutive waveforms exceeded 5% or if pulse wave amplitude was less than 80 mV. To calibrate the pulse wave, brachial blood pressure blood pressure was recorded immediately before the tonometric recordings. Systolic and diastolic brachial blood pressure was the average of three consecutive obtained readings, using a validated OMRON 705CP oscillometric sphygmomanometer (Omron Inc., Kyoto, Japan). A standard cuff of 22x12 cm with an inflatable bladder was used for subjects with an arm circumference of less than 32 cm. For greater arm circumferences, a cuff with a 35x15 cm bladder was used.

We used the carotid pressure waveform to derive central hemodynamic parameters. The software returns the central systolic blood pressure and the pressure at the first (P1) and second (P2) peak or shoulder of the carotid waveform. Pulse pressure was defined as the difference between central systolic and diastolic blood pressure. Mean arterial blood pressure was calculated as diastolic blood pressure plus one third of pulse pressure. Augmentation pressure was the difference between P2 and P1, and the augmentation index (cAI) was the ratio of augmentation pressure to central pulse pressure, expressed as a percentage. Aortic pulse wave velocity (PWV) was measured by sequential recordings of the arterial pressure wave at the carotid and femoral arteries as previously described (5). Distances were determined from the carotid sampling site to the suprasternal notch (distance A) and from the suprasternal notch to the femoral artery (distance B). PWV distance was calculated as distance B minus distance A. Pulse transit time was defined as the time interval between initial increase in carotid and femoral waveforms and was averaged over 10 consecutive beats. Aortic PWV was calculated as the ratio of the pulse wave distance (in meters) to the transit time (in seconds).

Other Measurements

At the examination centre, trained study nurses administered a questionnaire to collect detailed information on each subject's medical history, smoking and drinking habits, and intake of medications. Hypertension was a blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic (average of 5 consecutive auscultatory readings at the examination centre) or the use of antihypertensive drugs. Body mass index was weight in kilograms divided by the square of height in meters. Obesity was a body mass index of 30 kg/m² or higher.

Blood venous samples were drawn after overnight fasting, in which haematocrit, blood glucose, total cholesterol, serum sodium, serum potassium, serum uric acid (SUA) and serum creatinine were determined by standard clinical laboratory methods. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula (6). Renal failure was defined as an eGFR <60 ml/min per 1.73m² body surface in combination with a serum creatinine level >133 µmol/L for men and >124 µmol/L for women. Diabetes was defined as a fasting blood glucose level of more than 7.0 mmol/L or use of antidiabetic agents.

Reference list

(1) Salvi E, Kuznetsova T, Thijs L, Lupoli S, Stolarz-Skrzypek K, D'Avila F, Tikhonoff V, De Astis S, Barcella M, Seidlerová J, Benaglio P, Malyutina S, Frau F, Velayutham D, Benfante R, Zagato L, Title A, Braga D, Marek D, Kawecka-Jaszcz K, Casiglia E, Filipovsky J, Nikitin Y, Rivolta C, Manunta P, Beckmann JS, Barlassina C, Cusi D, Staessen JA. Target sequencing, cell experiments, and a population study establish nitric oxide synthase (eNOS) gene as hypertension susceptibility gene. *Hypertension* 2013; 62:844-852.

(2) Gottdiener JS, Bednarz J, Devereux R, Gardin J, Klein A, Manning WJ, Morehead A, Kitzman D, Oh J, Quinones M, Schiller NB, Stein JH, Weissman NJ; American Society of Echocardiography.American Society of Echocardiography recommendations for use of echocardiography in clinical trials. *J Am Soc Echocardiogr* 2004; 17:1086-1119.

(3) Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; 57:450-458.

(4) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a brang of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18:1440-1463.

(5) Liu YP, Thijs L, Kuznetsova T, Gu YM, Asayama K, Stolarz-Skrzypek K, Jin Y, Verhamme P, Struijker-Boudier HA, Staessen JA. Central systolic augmentation indexes and urinary sodium in a white population. *Am J Hypertens* 2013; 26:95-103.

(6) Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150:604-612.

Supplemental Table S1. Clinical characteristics of study participants by tertiles of the distribution of RRI

	Categories of RRI			
Characteristics	n=56	n=56	n=59	*P* value
RRI	0.537 ± 0.024	0.590 ± 0.011	0.663 ± 0.040	
Age, y	43.8 ± 11.0	49.3 ± 13.1	63.7 ± 9.1	<0.0001
Height, cm	174.8 ± 8.5	170.6 ± 9.2	165.7 ± 8.4	<0.0001
Weight, kg	82.2 ± 14.8	77.9 ± 13.6	77.2 ± 15.6	0.15
Body mass index, kg/m^2	26.8 ± 4.1	26.7 ± 4.0	28.0 ± 4.7	0.20
Systolic BP*, mmHg	122 ± 11	122 ± 16	136 ± 15	<0.0001
Diastolic BP*, mmHg	79 ± 9	78 ± 10	81 ± 8	0.32
Pulse pressure*, mmHg	43 ± 6	44 ± 9	55 ± 10	<0.0001
Mean arterial pressure*, mmHg	94 ± 9	93 ± 12	99 ± 10	0.002
Heart rate*, beats/min	61.3 ± 9.2	60.4 ± 9.0	59.5 ± 8.5	0.57
Questionnaire data				
Current smoking, n (%)	10 (17.9)	10 (17.9)	8 (13.6)	0.78
Alcohol use, n (%)	25 (44.6)	19 (33.9)	16 (27.1)	0.14
Treated for hypertension, n (%)	8 (14.3)	12 (21.4)	30 (50.8)	<0.0001
β-blockers, n (%)	2 (3.6)	5 (8.9)	18 (30.5)	<0.0001
Diuretics, n (%)	3 (5.4)	2 (3.6)	15 (25.4)	0.0003
CCB, n (%)	1 (1.8)	3 (5.4)	8 (13.6)	0.05
ACE or ARB, n (%)	4 (7.1)	3 (5.4)	10 (17.0)	0.08
Cardiac disease**, n (%)	3 (5.4)	0	6 (10.2)	0.05
Renal dysfunction, n (%)	0	1 (1.8)	7 (11.9)	0.02
Diabetes, n (%)	0	1 (1.8)	6 (10.2)	0.02
Biochemical data				
Hematocrit, %	42.5 ± 3.3	40.6 ± 2.8	41.3 ± 2.7	0.004
Blood glucose, mmol/L	4.69 ± 0.44	4.71 ± 0.53	5.07 ± 0.66	0.0002
Total cholesterol, mmol/L	4.78 ± 0.71	5.20 ± 0.98	4.88 ± 0.82	0.02
Serum sodium, mmol/L	140.0 ± 1.4	140.1 ± 1.8	140.3 ± 2.9	0.83
Serum potassium, mmol/L	4.43 ± 0.38	4.62 ± 0.37	4.50 ± 0.39	0.03
Serum uric acid, µmol/L	320 ± 76	313 ± 85	325 ± 86	0.74
Serum creatinine, µmol/L	79.1 (60.1-92.8)	70.7 (53.0-90.2)	69.8 (57.4-99.9)	0.24
eGFR, ml/min per 1.73m²	97.6 ±12.4	96.5 ± 16.7	81.2 ± 18.1	<0.0001

Values are mean±SD or number of subjects (%) or median (10%-90% percentile). *P* values are for the differences in prevalence rates or means across tertiles of the RRI distribution. *Blood pressure and heart rate were measured after echocardiographic examination in supine position. ** Cardiac disease included heart failure (n=2) and ischemic heart disease (n=7). BP, blood ressure; CCB, calcium channel blockers; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate.

Supplemental Table S2. Central hemodynamics, arterial and echocardiographic characteristics and renal length of study participants by tertiles of the distribution of RRI

	Categories of RRI			
Characteristics	n=56	n=56	n=59	*P* value
RRI	0.537 ± 0.024	0.590 ± 0.011	0.663 ± 0.040	
Sphygmocor measurements				
Central hemodynamics*				
Systolic blood pressure, mmHg	120 ± 11	121 ± 15	138 ± 22	<0.0001
Pulse pressure, mmHg	39 ± 10	41 ± 10	57 ± 18	<0.0001
Augmentation pressure, mmHg	10 ± 6	12 ± 8	23 ± 10	<0.0001
Pulse wave velocity, m/s	7.18 ± 1.45	7.30 ± 1.52	8.37 ± 1.57	0.0002
Echocardiographic structural indexes				
Left atrial volume index, ml/m²	22.4 ± 5.2	23.5 ± 4.9	28.7 ± 7.7	<0.0001
LV end-diastolic internal diameter, cm	5.06 ± 0.38	4.98 ± 0.44	4.95 ± 0.45	0.35
Posterior end-diastolic wall thickness, cm	0.97 ± 0.13	0.93 ± 0.12	1.00 ± 0.14	0.02
Interventricular wall thickness, cm	1.02 ± 0.16	0.98 ± 0.14	1.10 ± 0.20	0.001
LV mass index, g/m²	94.2 ± 20.6	91.5 ± 21.5	105.1 ± 25.1	0.003
LV outflow diameter, cm	2.20 ± 0.18	2.12 ± 0.19	2.12 ± 0.20	0.04
Doppler volume indexes				
LVOT peak velocity, cm/s	1.07 ± 0.15	1.12 ± 0.16	1.11 ± 0.19	0.30
LVOT VTI , cm	21.4 ± 3.20	22.7 ± 3.10	23.7 ± 4.22	0.003
LVOT stroke volume, ml	81.2 ± 16.5	81.2 ± 19.7	83.0 ± 21.1	0.84
E peak, cm/s	70.0 ± 15.5	70.7 ± 17.9	65.3 ± 17.0	0.17
E VTI, cm	9.45 ± 1.99	9.66 ± 2.09	9.12 ± 2.27	0.38
A peak, cm/s	53.3 ± 12.4	56.8 ± 14.5	68.2 ± 14.1	<0.0001
A VTI, cm	4.47 ± 1.19	4.79 ± 1.45	5.89 ± 1.32	<0.0001
E/A ratio	1.40 ± 0.52	1.35 ± 0.57	0.99 ± 0.30	<0.0001
TDI indexes				
e' peak**, cm/s	11.7 ± 3.5	11.1 ± 3.6	7.9 ± 2.3	<0.0001
a' peak**, cm/s	9.2 ± 1.9	9.4 ± 2.1	9.8 ± 2.0	0.37
E/e' ratio	6.28 ± 1.47	6.68 ± 1.73	8.81 ± 2.74	<0.0001
Renal ultrasound				
Renal length, cm	11.02 ± 0.64	11.01 ± 0.66	10.73 ± 0.88	0.06

Values are mean±SD. *P* values are for the differences in means across tertiles of the RRI distribution. *Measurements of central haemodynamics were available for 120 participants. **Averaged of septum, lateral, inferior and posterior mitral annulus sites. BP, blood pressure; LV, left ventricular; LVOT left ventricular outflow tract; VTI, velocity time integral; TDI, tissue Doppler imaging.

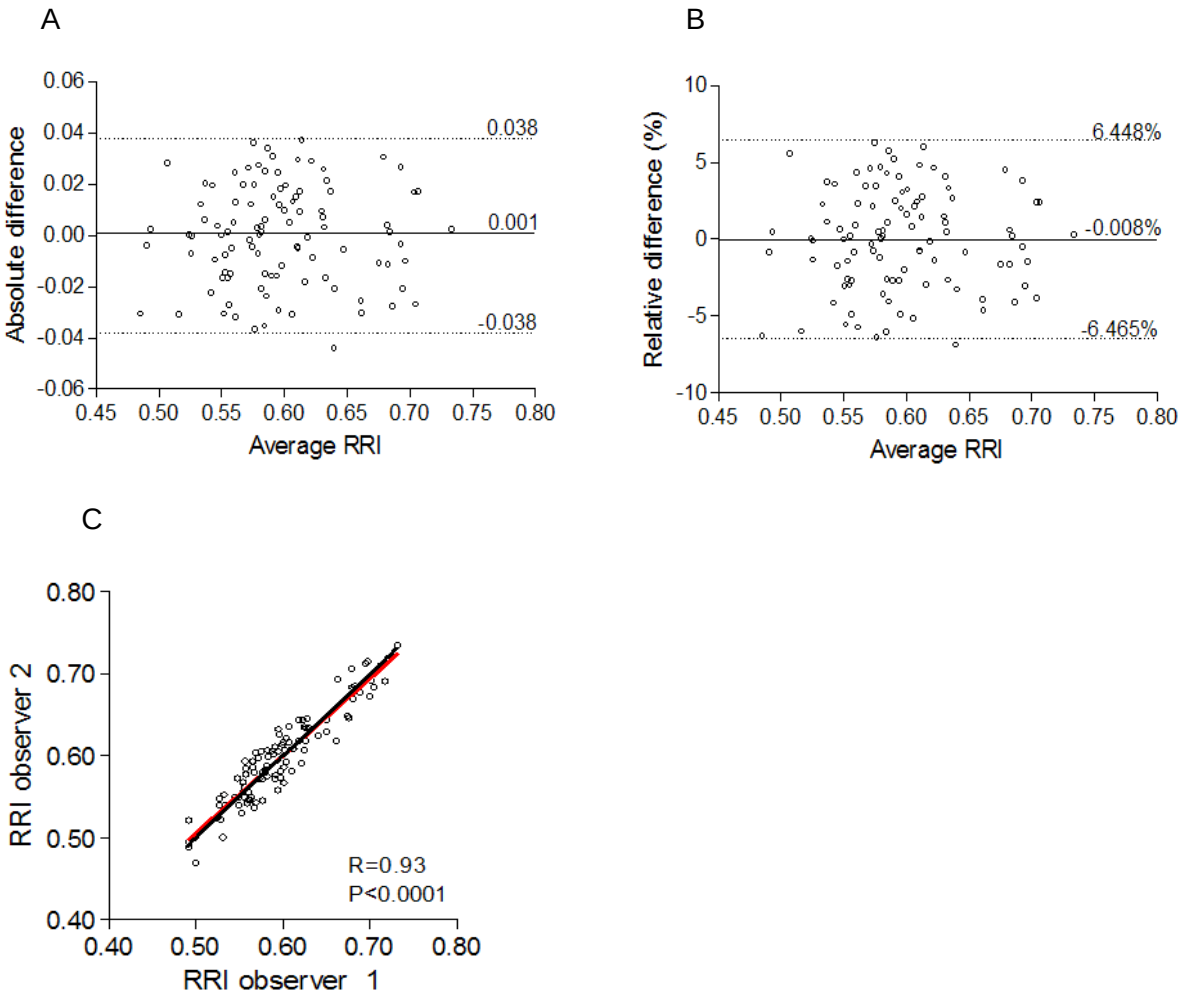
Supplemental Table S3. Multivariable-adjusted correlations of RRI with central blood pressure, arterial characteristics and echocardiographic indexes in untreated participants

	RRI		
Explanatory variables	Effect size	95% CI	*P* value
Central blood pressure and arterial characteristics			
Central systolic blood pressure (+17 mmHg)	0.019	0.0097 to 0.029	<0.0001
Central pulse pressure (+15 mmHg)	0.026	0.015 to 0.035	<0.0001
Augmentation pressure (+9 mmHg)	-0.0050	-0.019 to 0.009	0.49
Pulse wave velocity (+1.6 m/s)	0.0051	-0.0056 to 0.016	0.35
Echocardiographic structural indexes			
Left atrial volume index (+6.7 ml/m²)	0.0046	-0.0047 to 0.014	0.33
LV end-diastolic internal diameter (+0.43 cm)	-0.0056	-0.014 to 0.0025	0.17
Posterior end-diastolic wall thickness (+0.14 cm)	-0.0085	-0.018 to 0.00076	0.071
Interventricular wall thickness (+0.18 cm)	-0.0031	-0.013 to 0.0067	0.53
LV mass index (+23 ml/m²)	-0.0084	-0.018 to 0.0011	0.084
Doppler indexes			
LV outflow			
LVOT peak velocity (+17 cm/s)	0.0054	-0.00041 to 0.011	0.068
LVOT VTI (+3.7 cm)	0.0092	0.0030 to 0.015	0.0038
LVOT stroke volume (+19 ml)	0.0053	-0.0027 to 0.013	0.18
Transmitral diastolic inflow			
E peak velocity (+17 cm/s)	0.0097	0.0027 to 0.017	0.0072
E VTI (+2.1 cm)	0.0079	0.0011 to 0.014	0.023
A peak velocity (+15 cm/s)	-0.0072	-0.016 to 0.0024	0.14
A VTI (+1.5 cm)	-0.011	-0.022 to 0.00026	0.056
E/A ratio (+0.51)	0.013	0.0048 to 0.021	0.0022
TDI indexes			
e' peak velocity (+3.6 cm/s)	0.0076	-0.0036 to 0.019	0.18
a' peak velocity (+2.0 cm/s)	-0.0080	-0.015 to -0.00092	0.027
E/e' ratio (+2.4)	0.0086	-0.0019 to 0.019	0.11

Effect sizes and corresponding 95%CI are expressed for a 1-SD increase in the explanatory variables and were adjusted for age, sex, body height, body weight and use of β blockers. For central systolic blood pressure, adjusted model included diastolic blood pressure. For central pulse pressure, adjusted model included mean arterial pressure. For augmentation pressure and pulse wave velocity, adjusted models included both mean arterial pressure and central pulse pressure. For echocardiographic indexes, adjusted model included mean arterial pressure and brachial pulse pressure. RRI indicates renal resistive index; CI, confidence interval; LV, left ventricular; LVOT, left ventricular outflow tract; VTI, velocity time integral; TDI, tissue Doppler imaging.

Supplemental Figures

Supplemental Figure S1. Panels A and B show Bland-Altman plots with absolute and relative differences of pairwise RRI readings, respectively. Biases and 95% limits of agreement are represented by full and dotted lines, respectively. Panel C shows the correlation between pairwise readings of RRI done by the 2 observers. Black and red lines represent line of identity and correlation line, respectively.



Supplemental Figure S2. Univariate relation of RRI with age, body height, body weight, systolic and diastolic blood pressure and peripheral pulse pressure. Each panel shows the regression line, the Pearson correlation coefficient r and the corresponding *P* value. BP, blood pressure.